

نرمیتکم ریاس الشوائب

عشان اي شئ يدخل

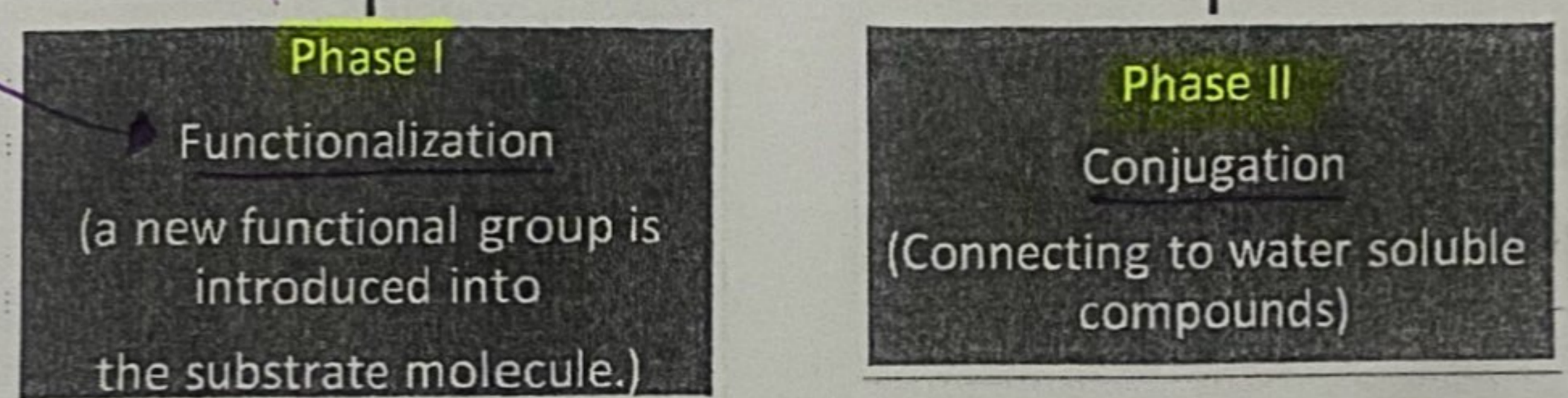
Drug metabolism

ع جسمه (not toxic)

- The aim of all drug metabolism processes is to **detoxify** the drugs, Very often these metabolites lose the activity of the original drug, but in some cases they may retain a certain level of activity.

ازالة السم
د بتخلون الجهر
منها عن طريق
- Kidney
- Feces,
ادق طريق
عن طريق البصق

Metabolism



لترتيب هولا (Phase I) زي بس خط ايدك مع لغير
نظ OH / NH / مع عربيه
حيث ايد الباب هاي ترتيبه عليا
molecule اكبر بل Phase II
وال water soluble لتزيد من
امكانه اخراج للمواد

Drug metabolism

- Major organ in (drug metabolism) is the liver
- Why we study metabolism?
- Detoxifications**: Drugs, plant toxins, food additives, environmental chemicals, insecticides, and other chemicals foreign to the body undergo enzymatic transformations that usually result in the loss of pharmacological activity
- Bioactivation**: enzyme-catalyzed reactions may lead to the formation of a metabolite having therapeutic or toxic effects (as in prodrugs)

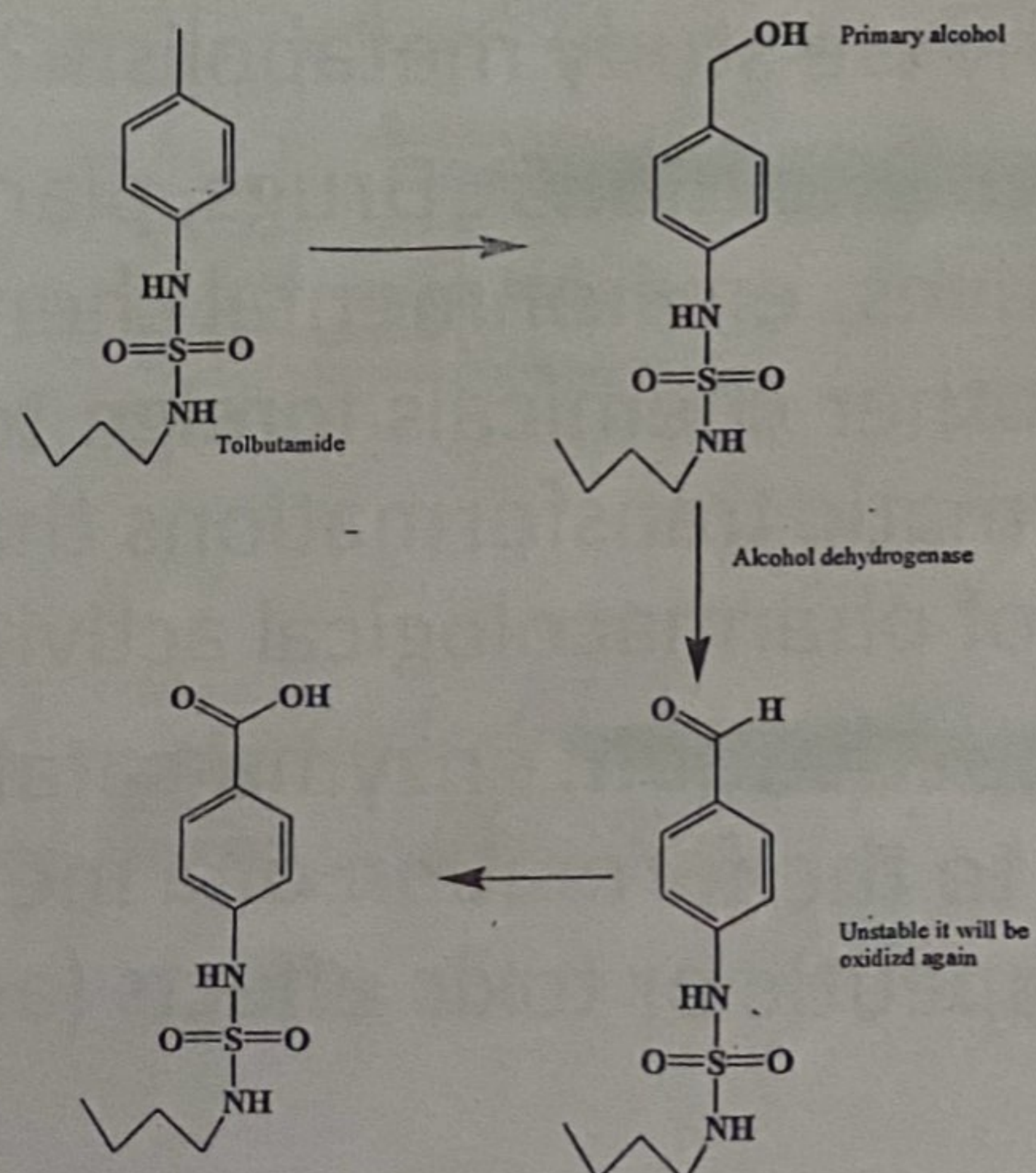
Phase-II metabolism

- Phase 2 Reactions (Conjugations): a functional group, such as **alcohol, phenol, or amine**, is masked by the addition of a new group, such as **acetyl, sulfate, glucuronic acid, or certain amino acids**, which further increases the polarity of the drug or xenobiotic.
- Phase-II metabolism involves the following conjugation reactions that are catalyzed by transferase enzymes:

- (1) — Glucuronidation.
- (2) — Sulfation.
- (3) — Amino acid conjugation.
- (4) — Methylation.
- (5) — Acetylation.

Example on benzylic oxidation (Tolbutamide)

- So Tolbutamide will be eliminated in urine:
- 1. Alcohol
- 2. Carboxylic acid
- 3. Conjugated



Phase II reactions

Phase II reactions

- Reactions which conjugate the drug or its phase-I metabolite with a hydrophilic, endogenous species (conjugation reactions).

لا يمكن هدم الدواء الى حيث موجوده
اصلاً في جسم الإنسان.

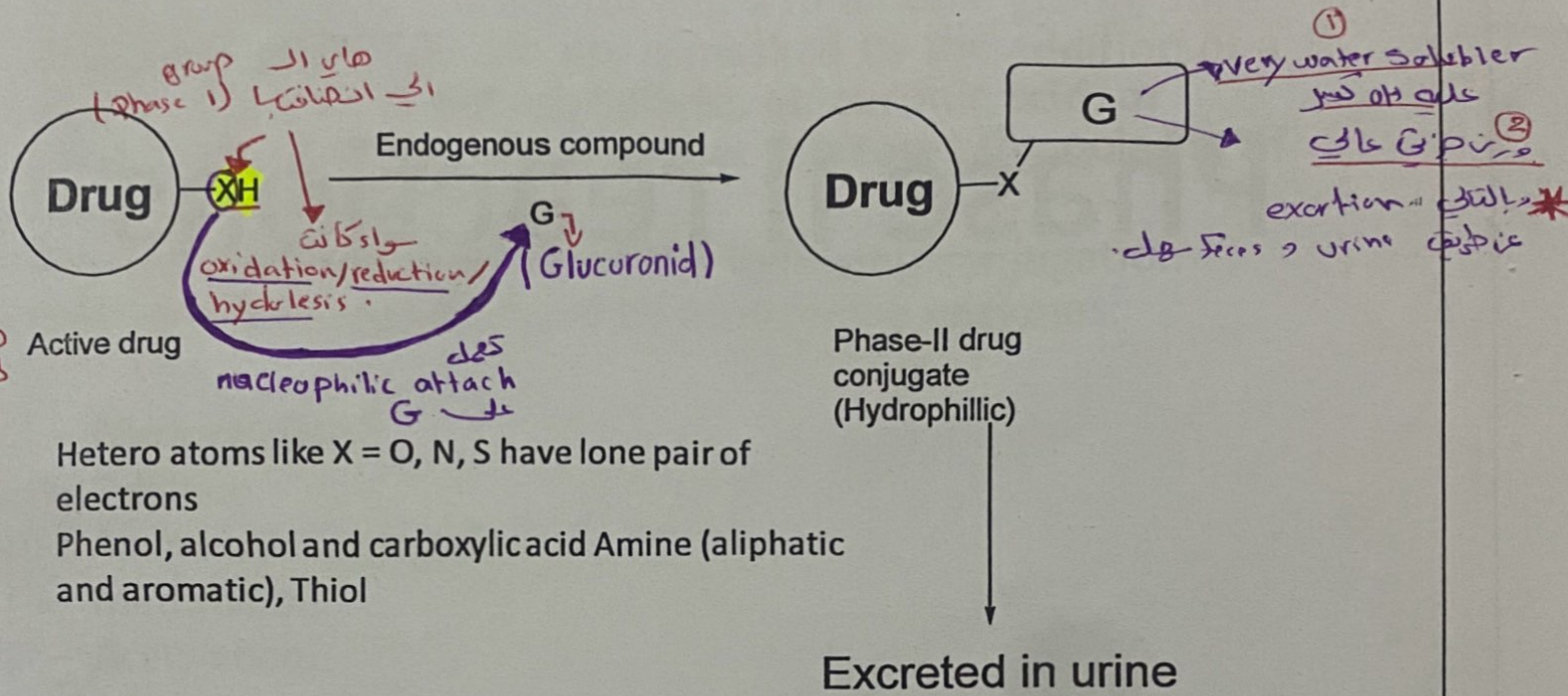
- These endogenous compounds are:

- ① Glucuronic acid
 - ① its very water soluble, and will be quickly renal eliminated because في ارجو ان يخرجها الى خارجة
 - ② also the moiety attached weight is 94 Daltons so it will be trapped in the renal tubules. making
- ② Sulfate group
- ③ Amino acid (Glycine) it better candidate for biliary elimination. making
- ④ Methyl group (as SAM)
- ⑤ Acetyl group (as acetyl CoA)
- ⑥ Glutathione (tripeptide)

زيادة الوزن الجزيء 94 بأنه عن الإفراج

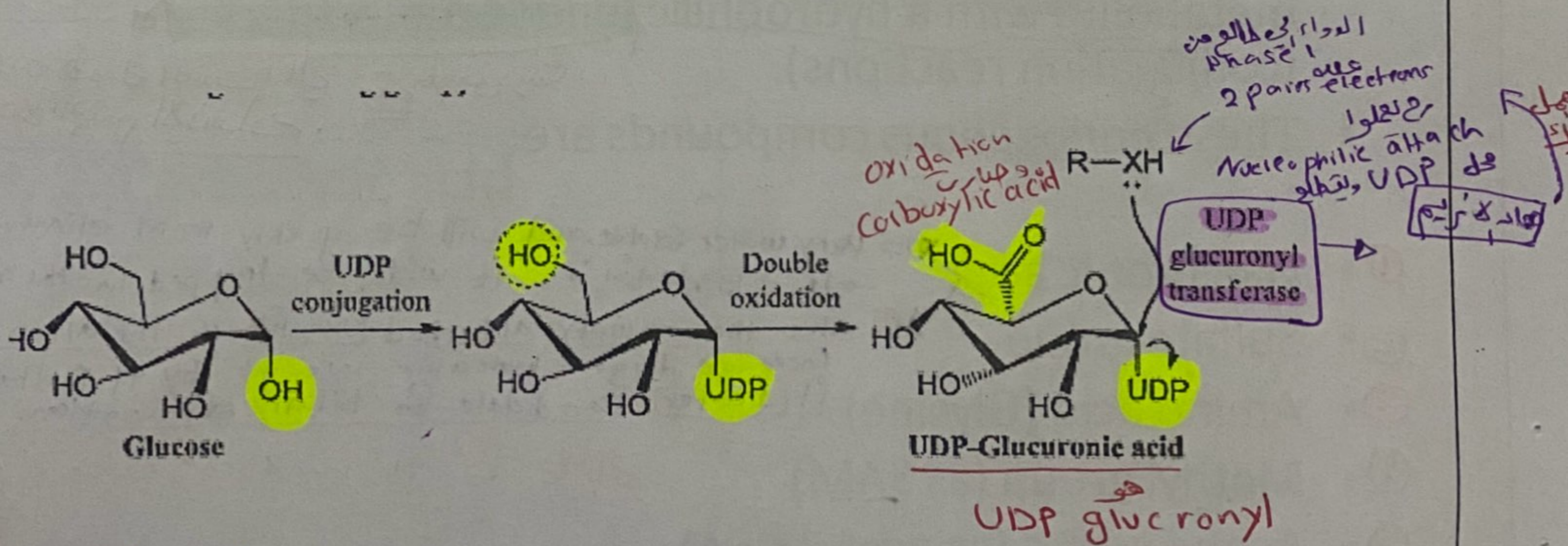
التي عن طريق
القنوات المرارية
بالماء الطبيعي
والتالي هو
إفراجه عن طريق
Feces.

Aim of Conjugation



From Glucose to UDP glucuronyl transferase

* UDP:- [uridine diphosphate]



* الفرق بين ال glucose و Glucuronic acid ال active form

1) OH oxidation carboxylic acid

2) UDP ال ائتلاف

Mechanism of conjugation

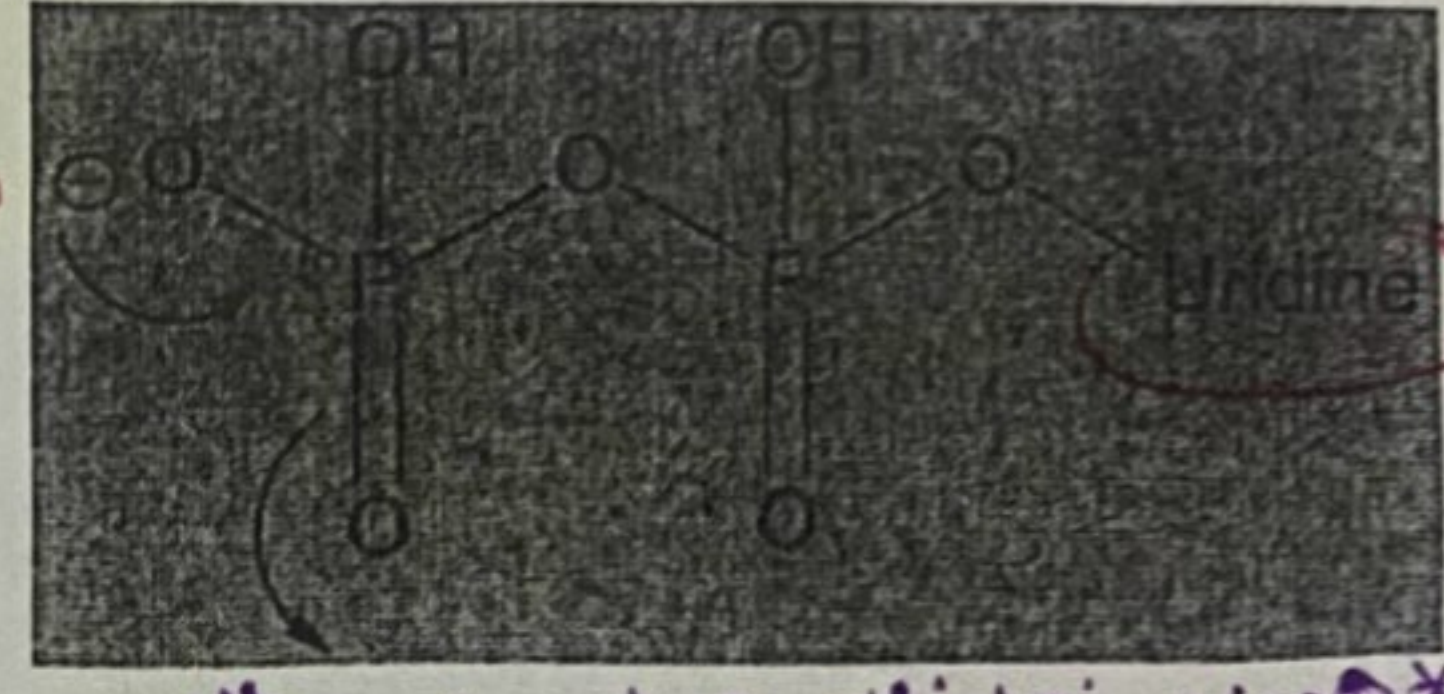
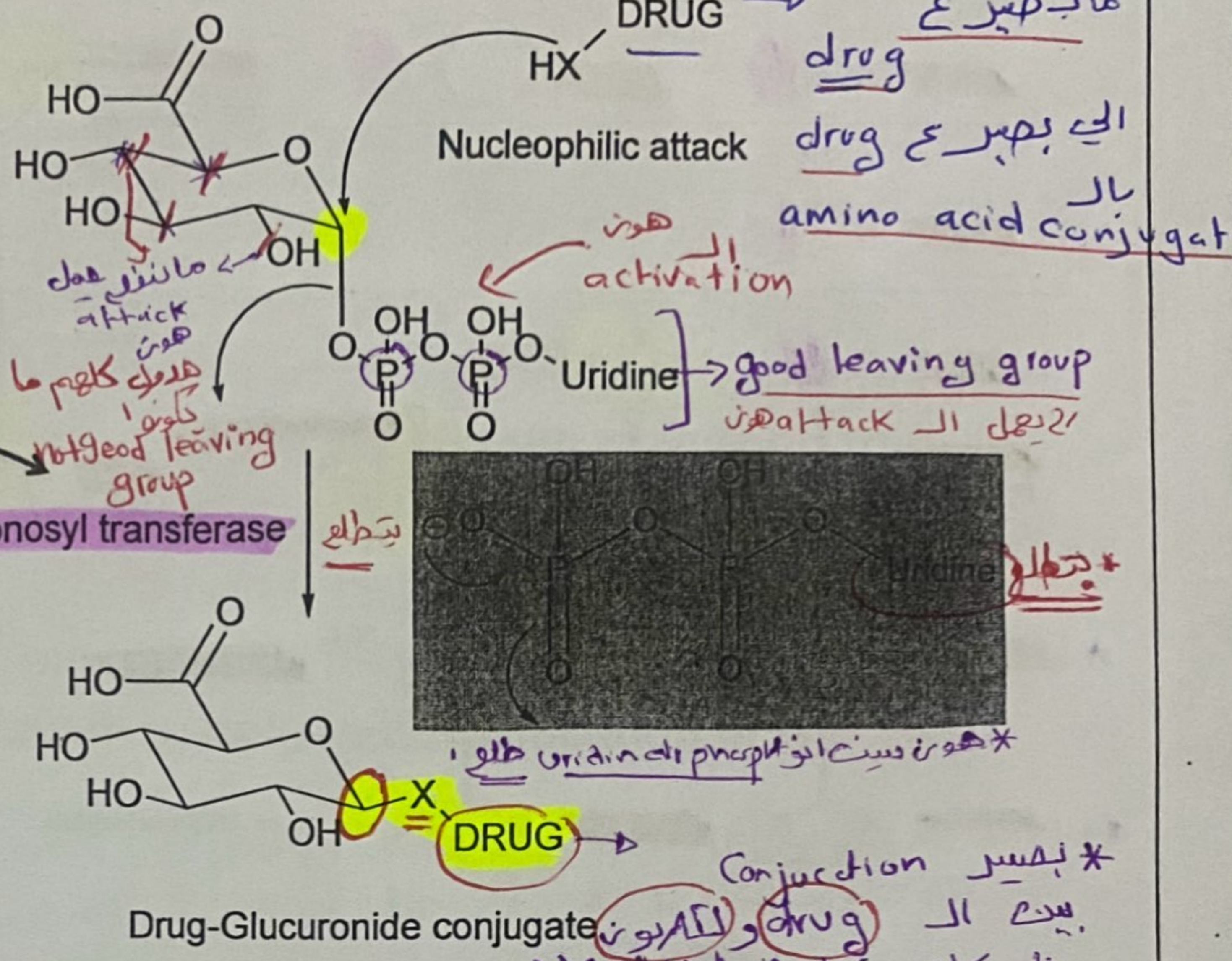
Glucorodination reaction

* النقص في UDP-glucuronosyl transferase
تسبب في حالة الصفار التي تتكون
عند الأطفال، لفكرة انه الاطفال او ما يتولد
الانزيمات تامة الكبد ما تكون متكاملة،
عند تولد الطفل هناك نقص عند لقائه
بمواد الانزيم

The deficiency of this enzyme in neonates causes Jaundice

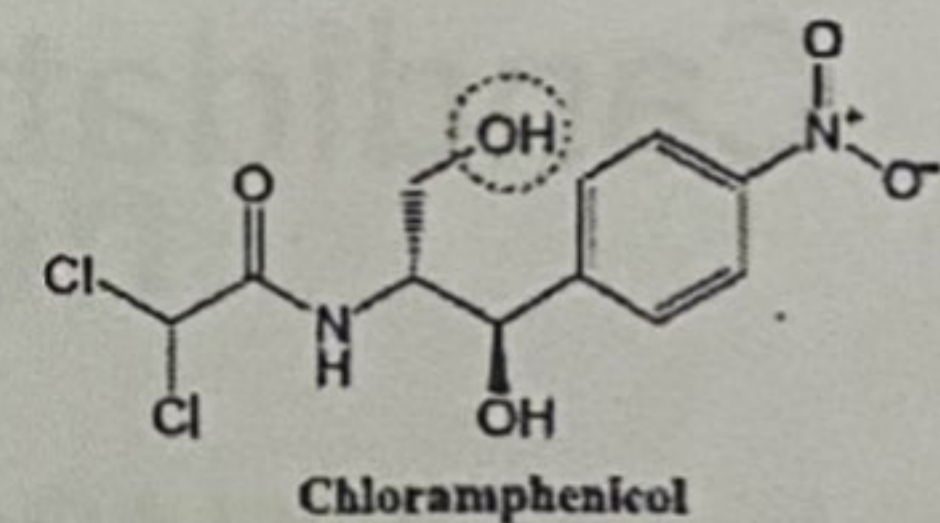
UDP-glucuronosyl transferase

* حينئذ يس يتخلص من السموم
كحان يعمل مع يتخلص من السموم الصفراء
الي بصنعها الكبد.



ال (Uridindiphosphate) غير (X)

Chloramphenicol



- Sometimes **UDP-Glucuronyl Transferase** enzyme is deficient in the newborns that their livers are immature after delivery which results in "**Neonate Jaundice**", in those babies any drug that needs to be conjugated in order to be eliminated will accumulate in their bodies.
- For example "**Chloramphenicol**", an antibacterial agent has two alcohols that can be conjugated so if there is no enough glucocornide conjugation due to problems in the liver, "**Grey-Baby syndrome**" will be result (Babies that have immature livers with little amount of UDP-Glucuronyl Transferase enzyme so they tend to accumulate
- Chloramphenicol in their bodies and terminating at Grey color).

* Grey Baby Syndrome :-

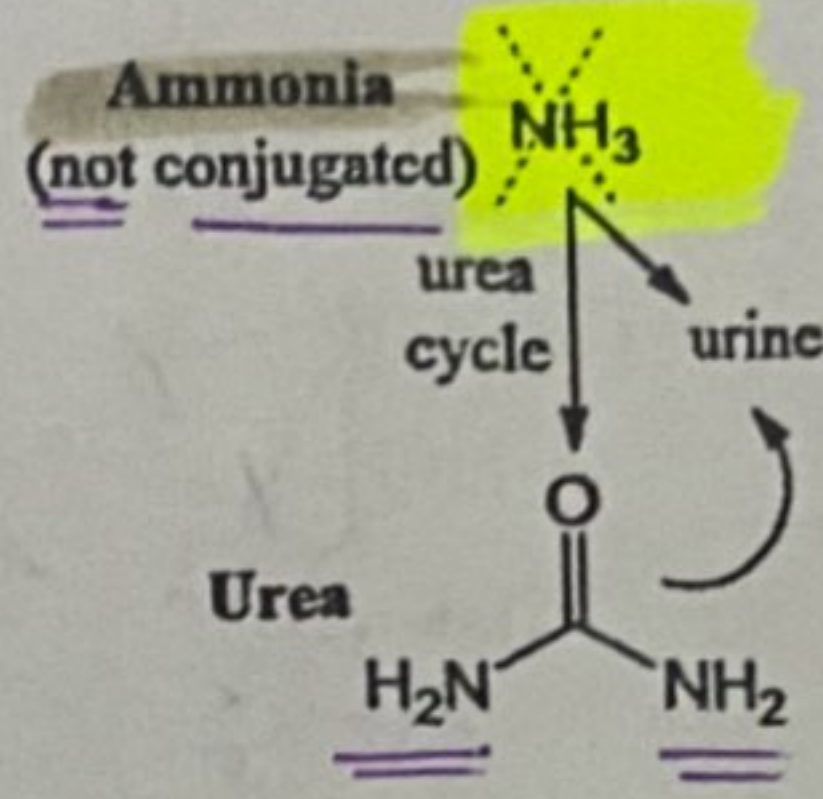
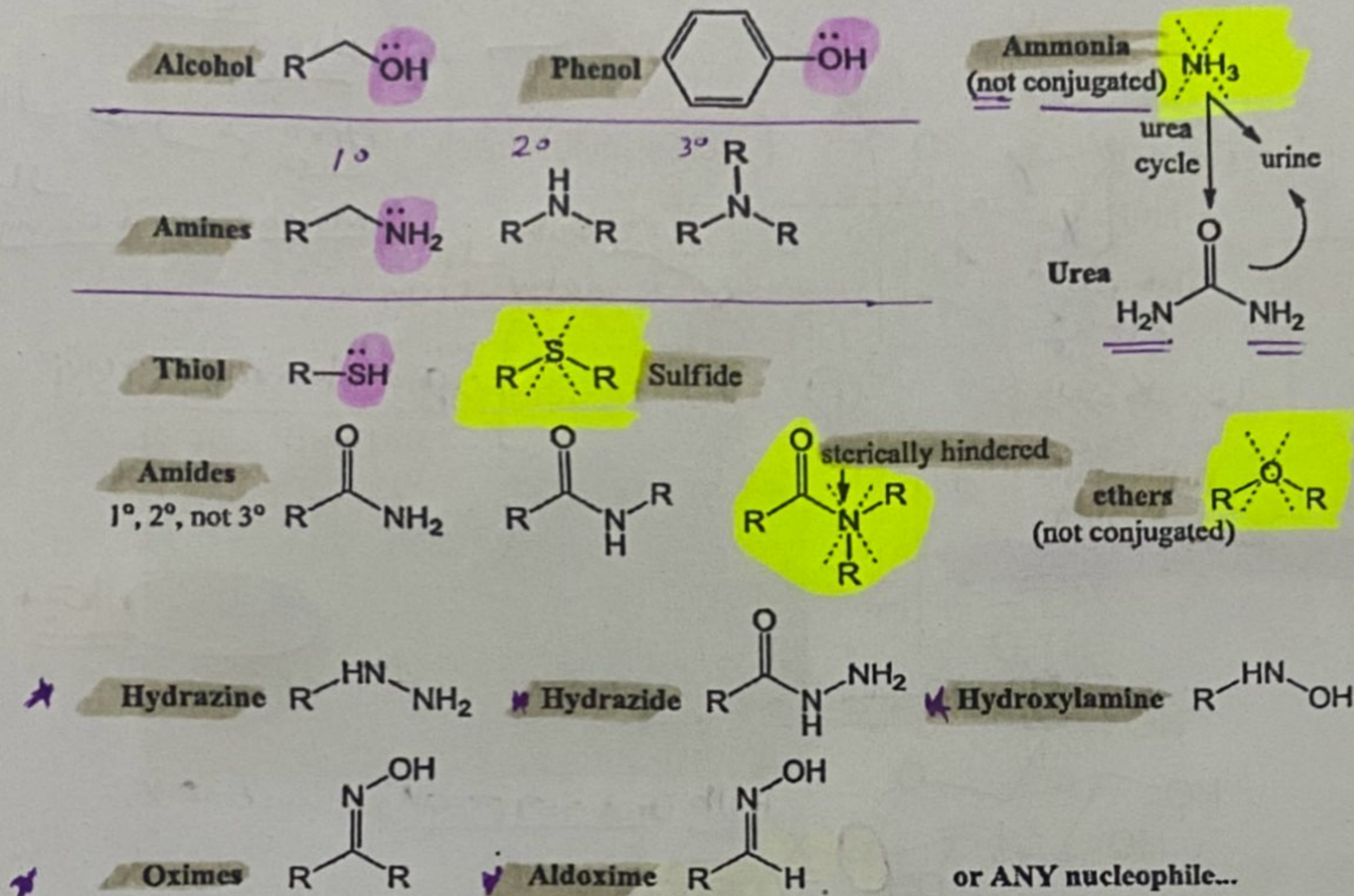
اهنطرابه يصيب الاطفال الرضوع فتجدهم د الفعل المكسب لتناول الام او لبنيين دوا Chloramphenicol
فحينئذ لا توجد انزيمات لازمه لكسر جزيئات الدواء عندهم و الاطفال فيتراكم في الدم مما يؤدي الي نقص
الاكسجين بالدم و انخفاض ضغط الدم وبالتالي يولد الطفل ملون بالبشرة الرمادية.

Gray baby syndrome



Candidates for Glucurodination reaction

Groups conjugated to Glucuronic acid

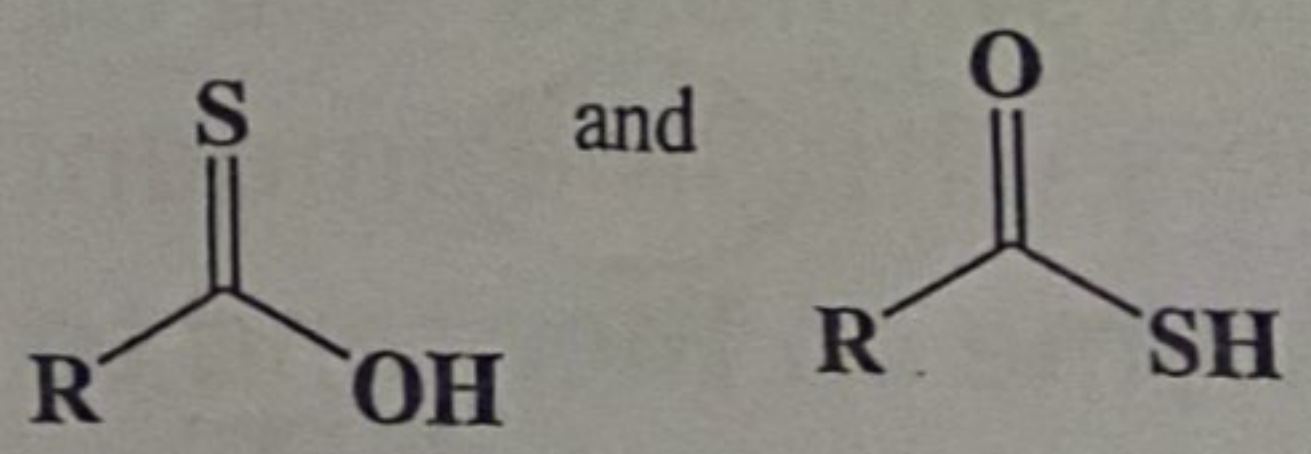


All the nucleophiles can be conjugated to the Glucuronic acid $(NH/OH/SH)$

جميع الكواشف التي لها ذرات الأوكسجين والهيدروجين على جزيء الجلوكورونيك
 Glucurodination على

Candidates for Glucurodination reaction

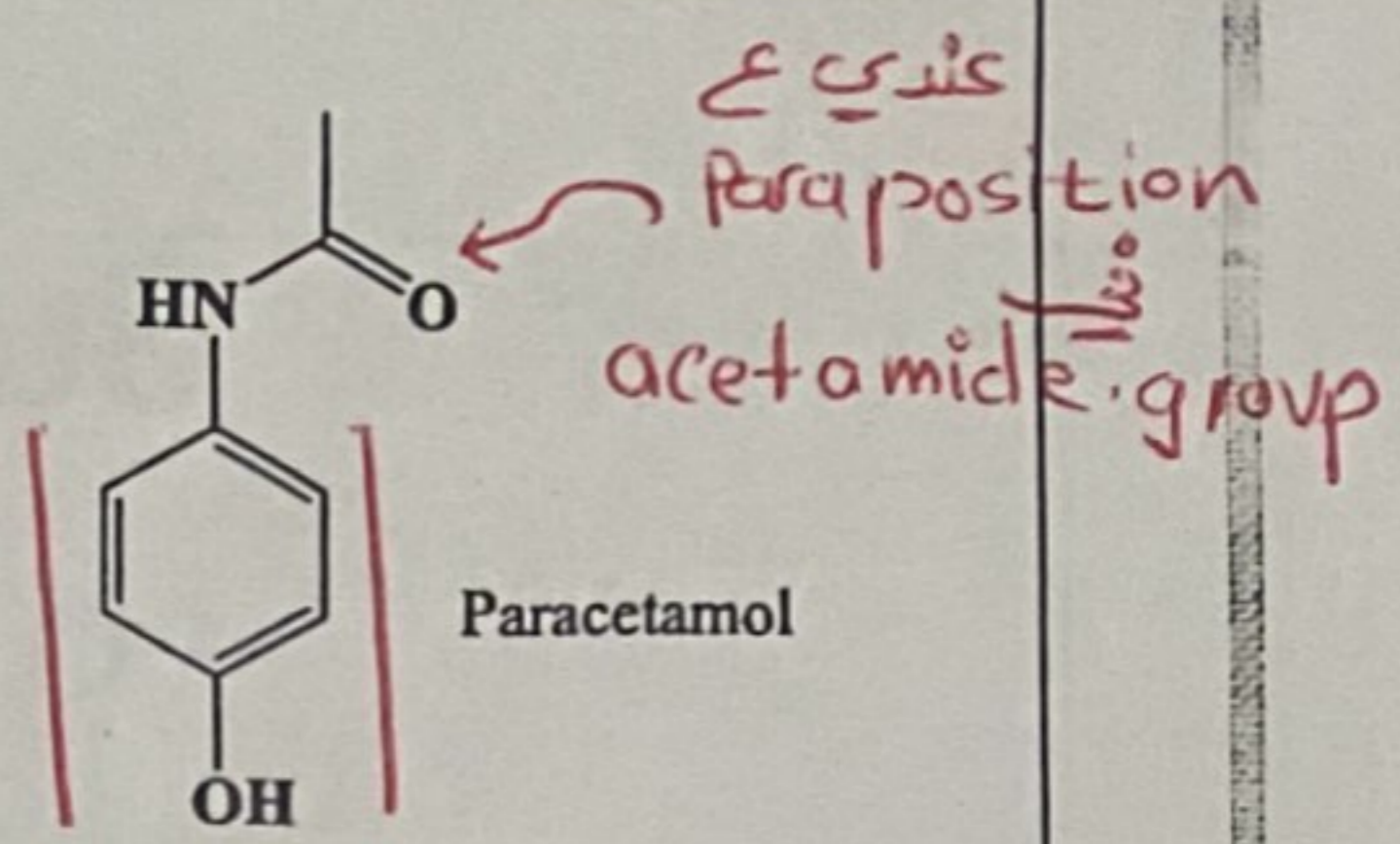
- 1. Aliphatic alcohols, Aromatic alcohols (Phenols)
- 2. Aliphatic amines, Aromatic Amines
- 3. Carboxylic acids
- 4. Thiols sulfide
- 5. Amides 3° also
- 6. Thioacids (it's abundant in liver)



Paracetamol toxicity

← مرتبط بـ
Glucuronidation
Sulfation
بجسم الإنسان

بجسم الإنسان
glucuronidation
Phenol group

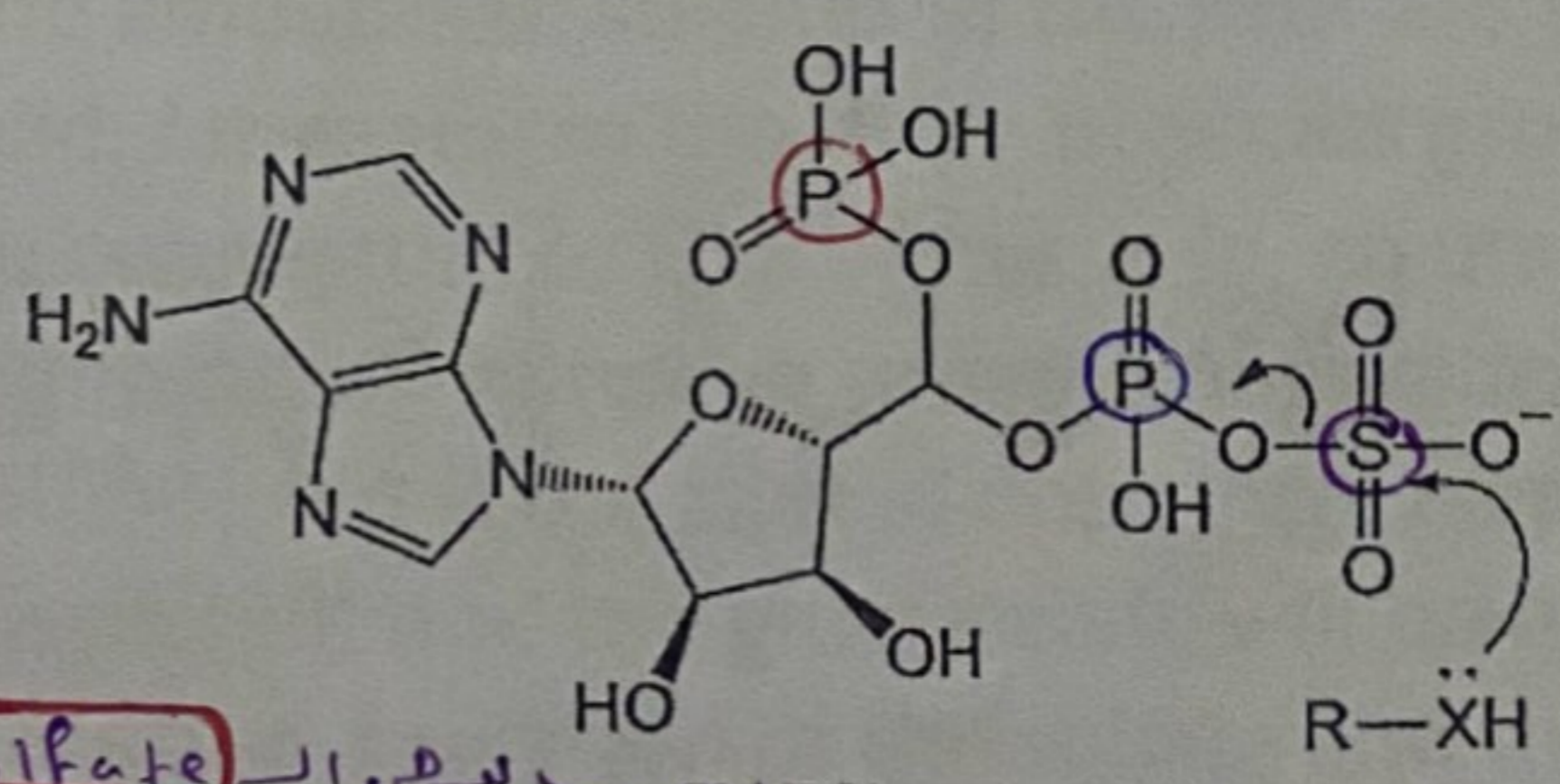


- The **Glucuronic acid stores are large stores in the liver** although they can be consumed and **cause toxicity**.
- After administration of **large toxic dose** of certain drug, for example if a patient administered **[20 tablets]** of **Paracetamol** at once (each tablet contains **500mg** so **20 tablets** contain **10g**), it can reach the **toxic dose** because it depleted all the **Glucuronic acid stores** and therefore it will start having toxicity, **But** **under normal clinical doses** usually the amount of **Glucuronic acid is enough to help in detoxification** of the drugs.

* لا وارد أخذ 20 حبة من Paracetamol مع كل واحد كل glucuronic وكل Sulfat في نصف الكبد مستنزف في انزيماته، وبتصير عننا حالة اسهال (تشمع الكبد) وروح يصير الكبد بجبال (Irreversible)

Sulfate conjugation

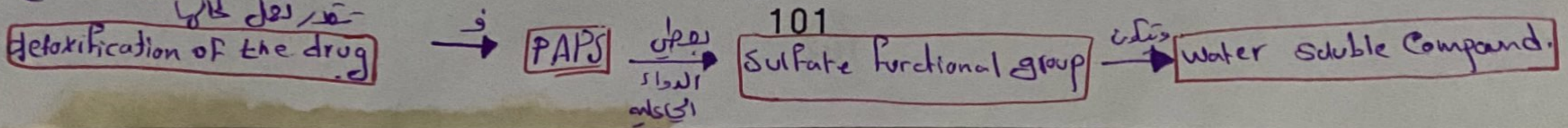
- Phospho adenosyl phospho sulfate PAPS**, and is the form added to **nucleophiles** in the **conjugation reactions** (the **liver** uses it to add **sulfate** to different nucleophiles).



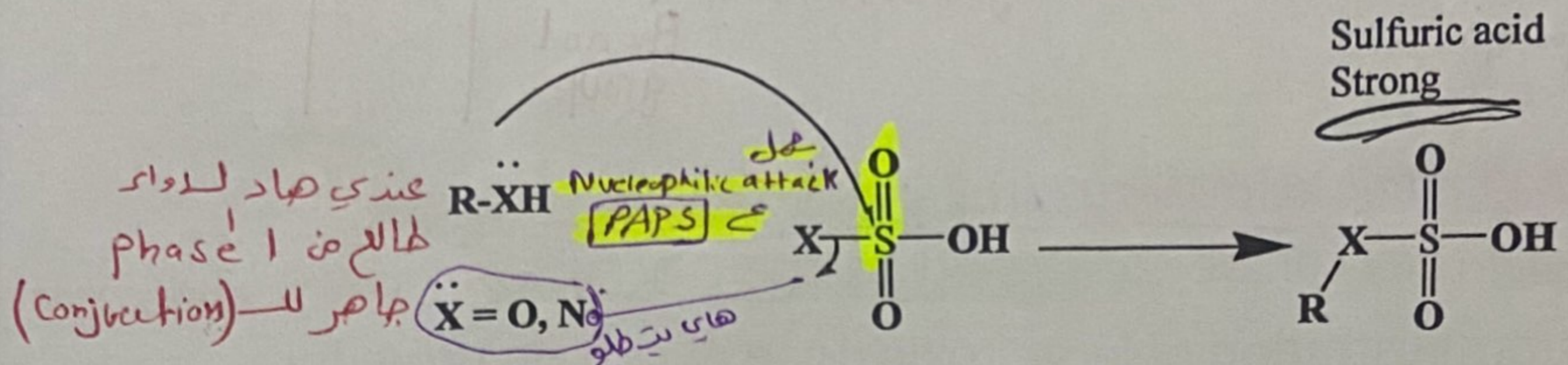
* Sulfate donor is **PAPS** (Phosphorylated Adenosine phospho sulfate)

(PAPS) سلفات من هاد
Sulfate مصدر ال
Phosphoadenosine 5'-phosphosulfate (sulfate source)

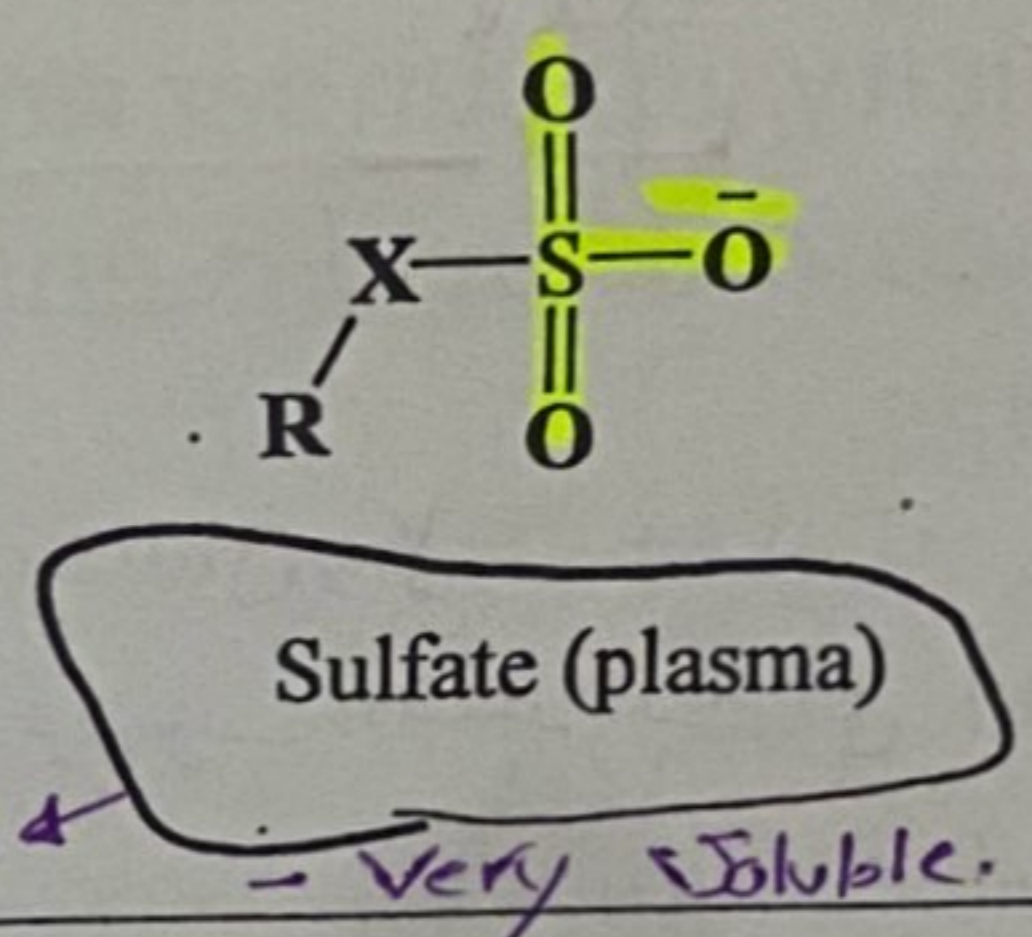
صغير وقيل حبة
وتخلص بسرعة
فاذا أخذ جرعة عالية من الدواء
ال Sulfate كالمها متلازم
تقل كالمها



Sulfate conjugation



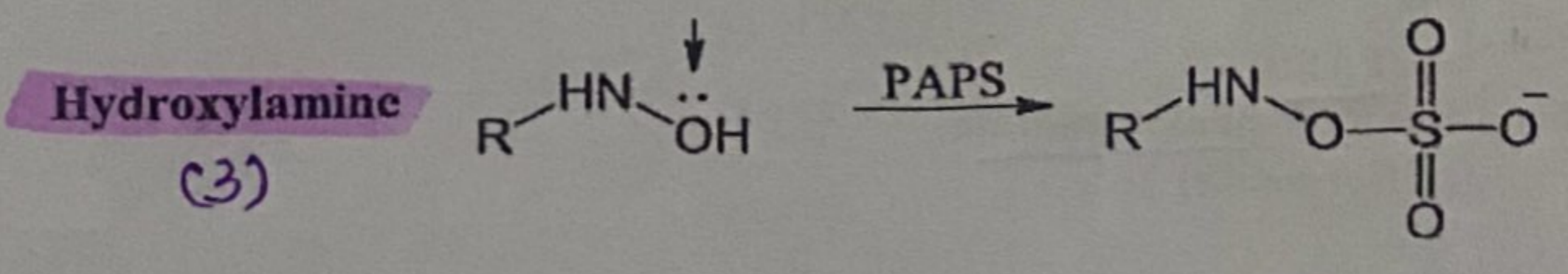
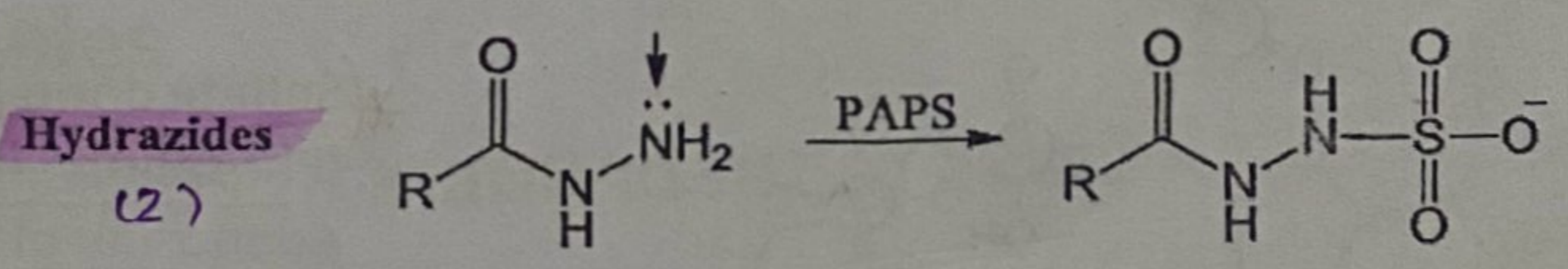
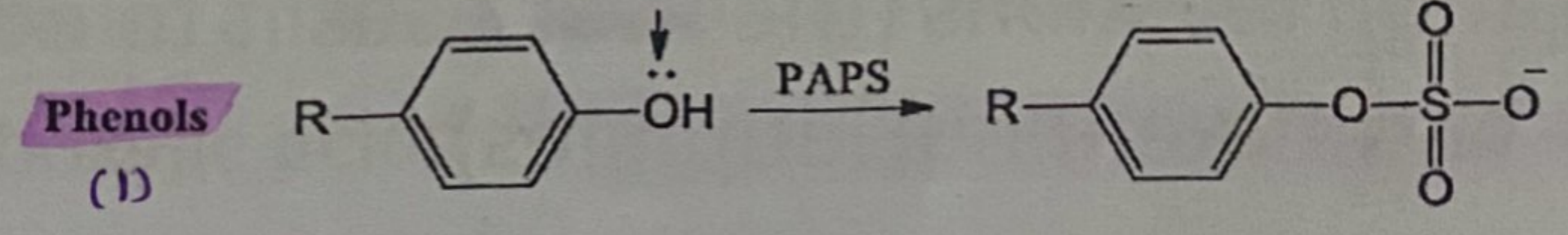
This acid is found in plasma in the form of sulfate, which can be eliminated in the urine, cause it's ionizable



اذا التقيت مع أي مرتب مع لي صير soluble
 واخرجه عن طريق ال urine
 كثير

Candidates for sulfation

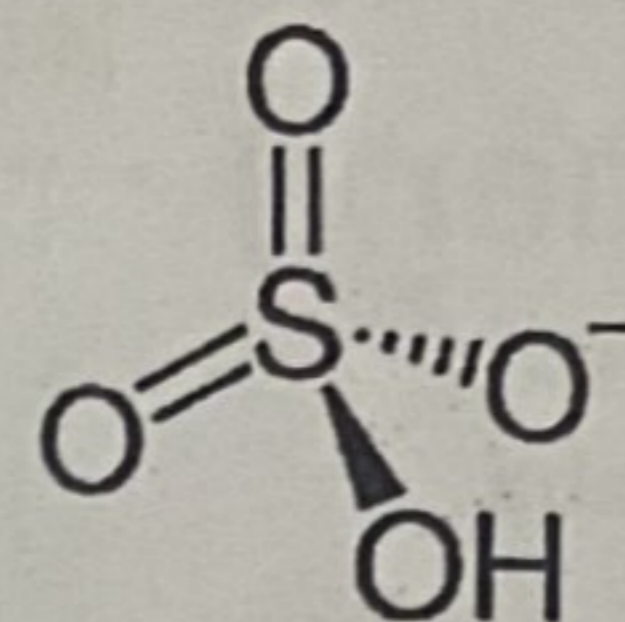
* بره تو يصر على
 Glucurodination
 س ال
 Sulfation
 كاله
 (limited sources)



Candidates for sulfation

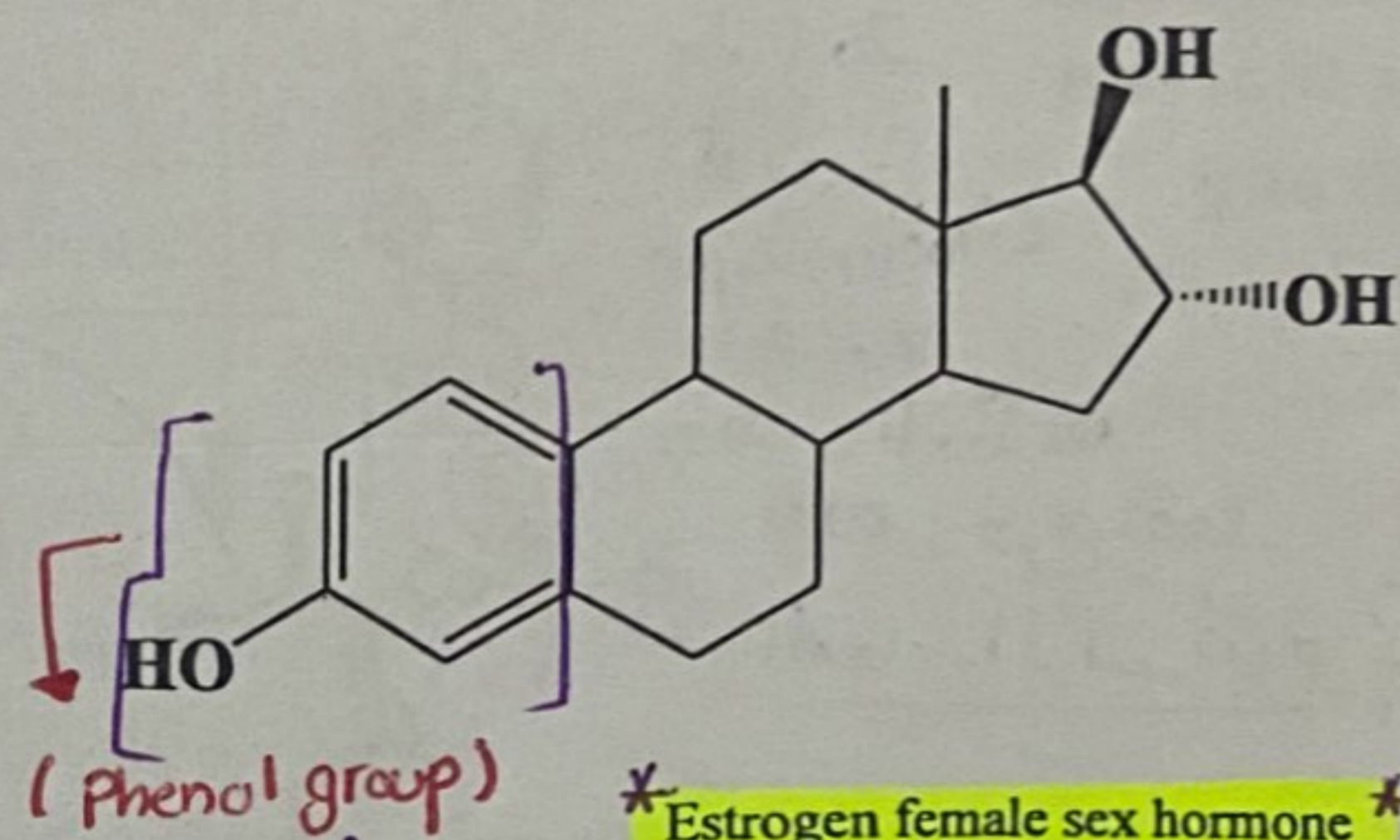
بهيير ع هودك (Sulfation) ->

1. phenols (Aromatic alcohols) (not aliphatic)
2. Anilines (Aromatic amines) (not aliphatic)
3. Hydroxyl amines



Majority of the sulfation process happens on the internal substrates like: (Bile salts, steroidal hormones such as testosterone, estrogens)

اذا اخذنا عينه جوه عن بارة رح نلاحظ انه رح يطلع estrogen على sulfate و عليه (glucuronin)

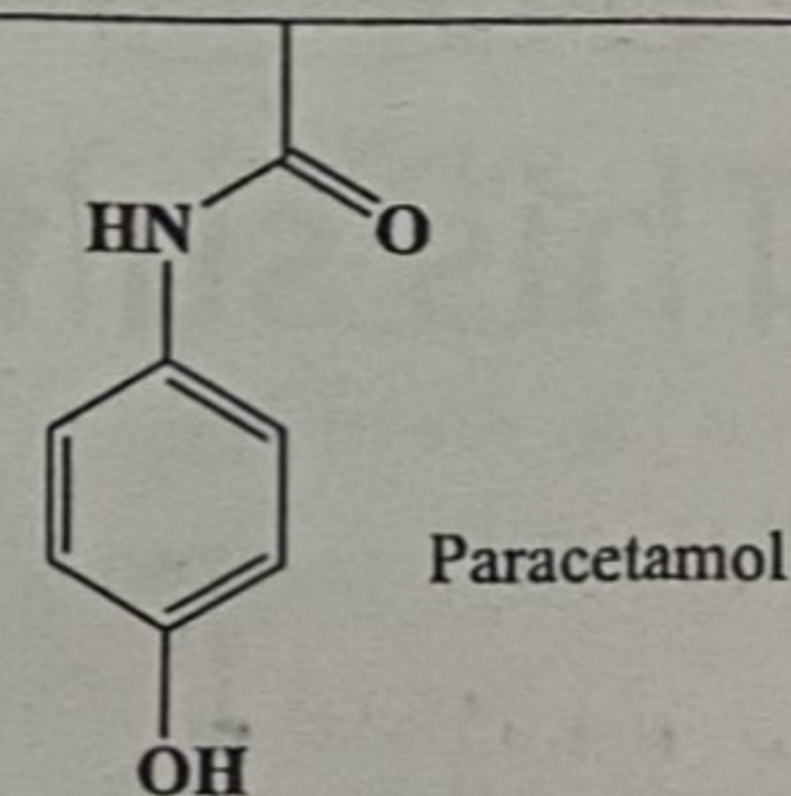


* Estrogen female sex hormone *

لسهول بهير عليها
Glucurination
Sulfation

* تراا القود مع Paracetamol صين هله

Paracetamol



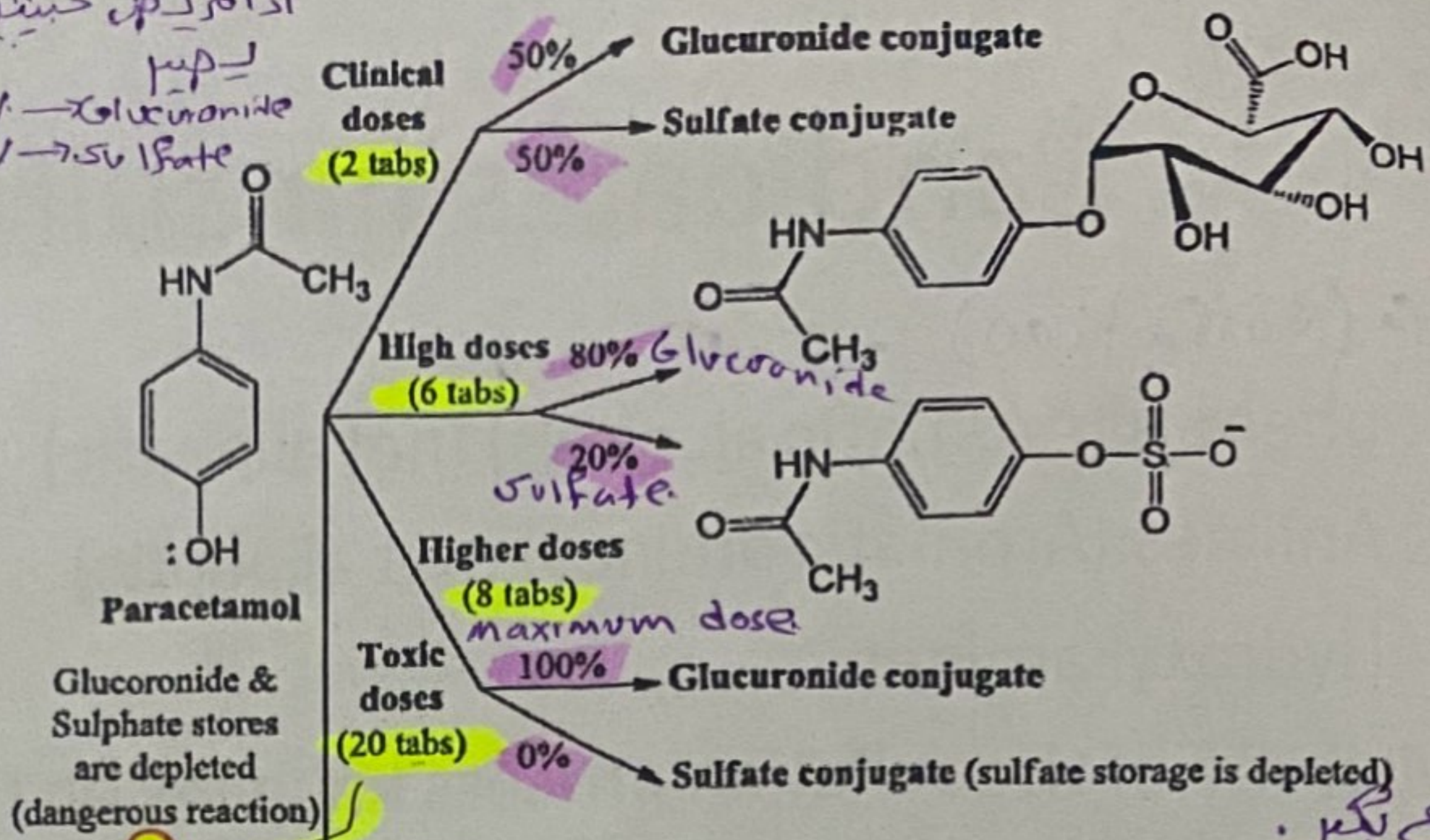
Paracetamol

- If taken in a clinical low dose we will see it in the urine as follows:
- 1. 50% Sulfate conjugate
- 2. 50% Glucuronide conjugate
- If the dose is high the majority of the dose is excreted as Glucuronide conjugate
- The amounts of sulfates in the liver are much lower than the Glucuronic acid, for example the three previous groups that can be sulfated also can be conjugated to Glucuronic acid, so under low clinical doses there is a competition between sulfate conjugation and glucuronide conjugation (50:50), but if the clinical dose increases the sulfate will be reduced (depleted) and the glucuronide will be higher than it (higher clinical doses results in depletion of the sulfate and therefore the glucuronide will be higher than the sulfate).

Paracetamol metabolism (Summary)

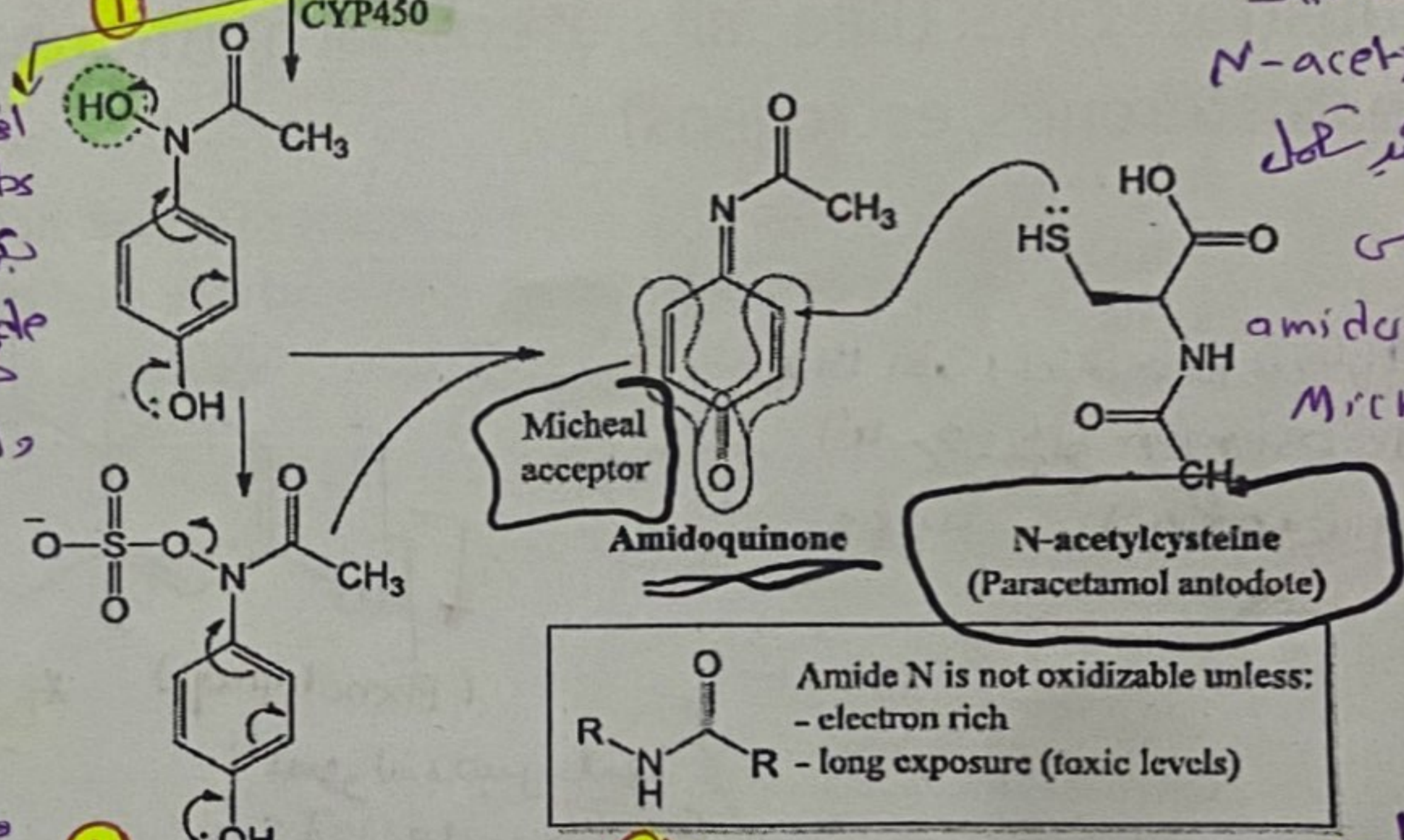
Reference: Prof. Taha

اذا زاد الجر حينئذ يرج
ليزيد
50% → Glucuronide
50% → Sulfate



Micheal acceptor is a very reactive and very toxic that can react with any nucleophile

اذا اخذ
20 tabs
تكون
Glucuronide
حلقة
والتفاعل
فلهذا فترقة
الدواء بالكبد فترقة
الزيتان



Amide N is not oxidizable unless:
- electron rich
- long exposure (toxic levels)

اذا حقوا المريض مع نيكتر
بفطوا N-acetylcysteine
فيل ما خلايا الكبد لجل
Nucleophilic
amidoquinone
ال Micheal acceptor
هو اليه اليه لجل
Nucleophilic

عز ترقيم
الاسم
امشوا

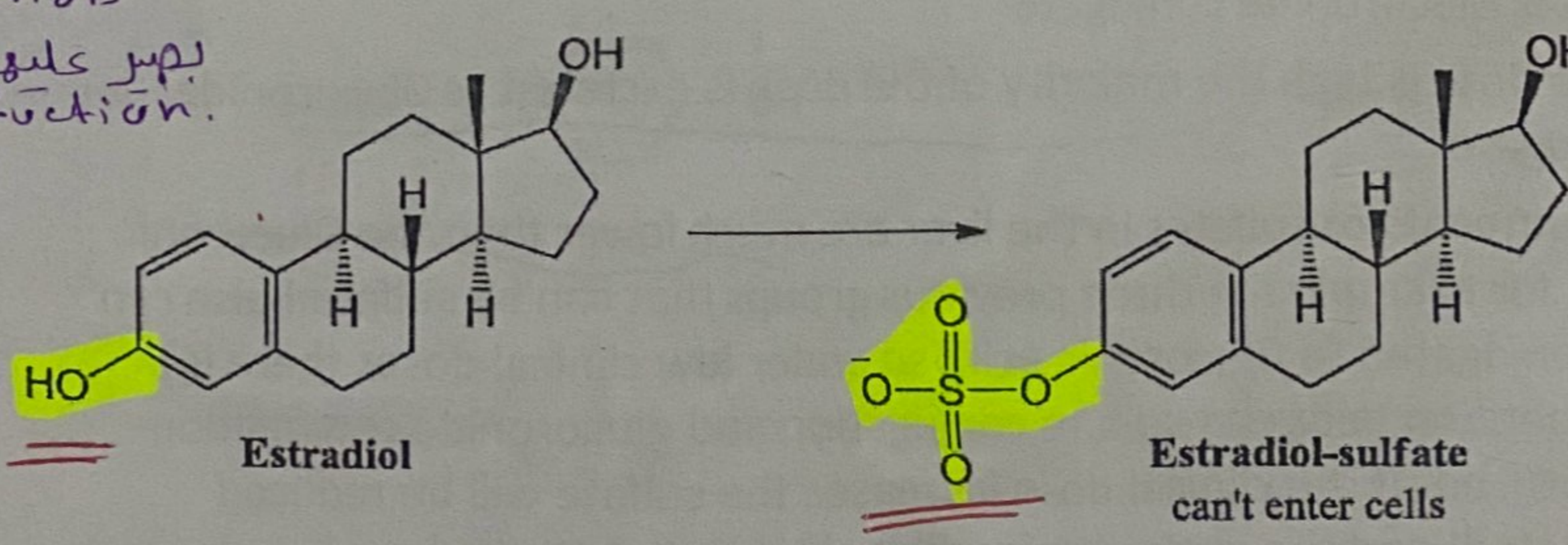
CYP450
oxidation
(حفاظة + HO)

وهذا الاشبه فطير لانه فاد

oxidation
الميكال اكواسي
مicheal acceptor
هو خطر كثير كثير
Nucleophile
covalent bond
irreversible
الوجود في خلايا الكبد
ويعمل الميكال اكواسي
Nucleophile
covalent bond
irreversible
وهذا المصيبة !!!
لانه ال covalent bond
تكون irreversible
وبهذه الطريقة
خلايا الكبد تفسد
هل تاتي غير
زرارة كجد

This sulfation is very important for some hormones

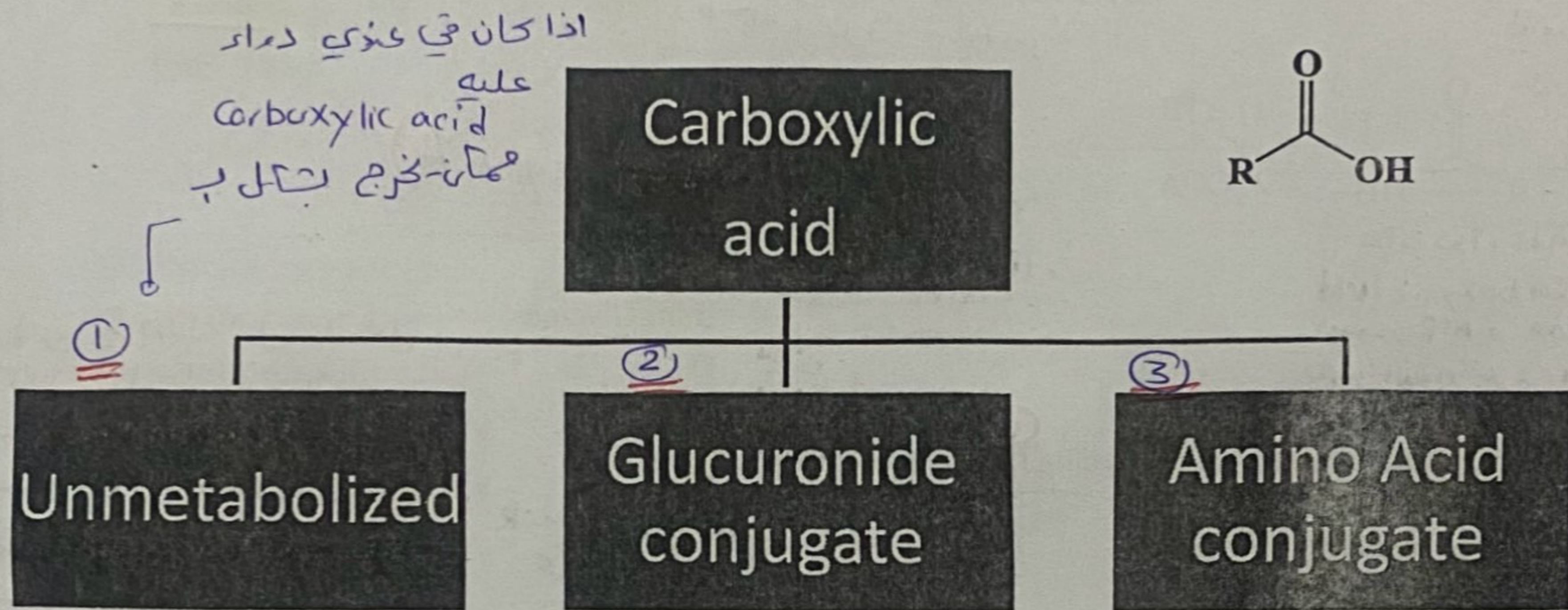
هاد لستادير بينا
بعض الهرمون
اليه عليها
Phenols
بغير عليها
Sulfuration.



هو الشرط ليعمل ال
anti dote
بعضه ليعمل مبكر
فلهذا كبرو راج
بعضه... لووو
كقنار المريضة
كله واعطينا ال
N-acetylcysteine
هيكه ليقدر يبتلق
المريض بونبقا
كبله المريضة

Water soluble. Metabolism. Carboxylic acid. Note

Fate of carboxylic acids in the body



Salicylic acid

سبب لو أخذوا عنه جوك للمريض أخذ

ح يكون فيها:

① salicylic acid unmetabolized

② Glucuronidated salicylic acid

③ Amino Acid Conjugate.

Acylation reactions

نتيجة ل رابع تفاعل
من تفاعلات ال
Conjugation.

Candidates for this reaction

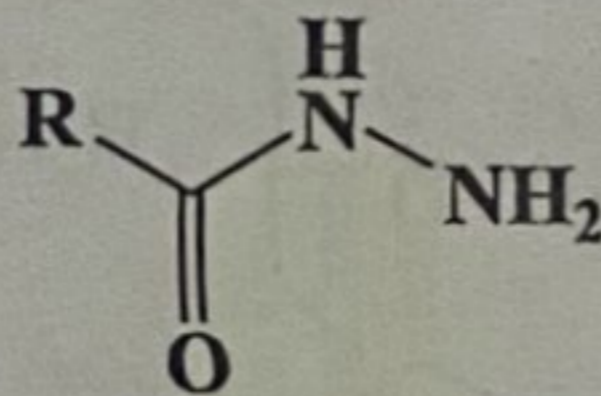
بصير على

1. Aromatic amines → Sulfonamide
بصير على

2. Hydrazines → Isoniazid
بصير على

3. Hydrazides

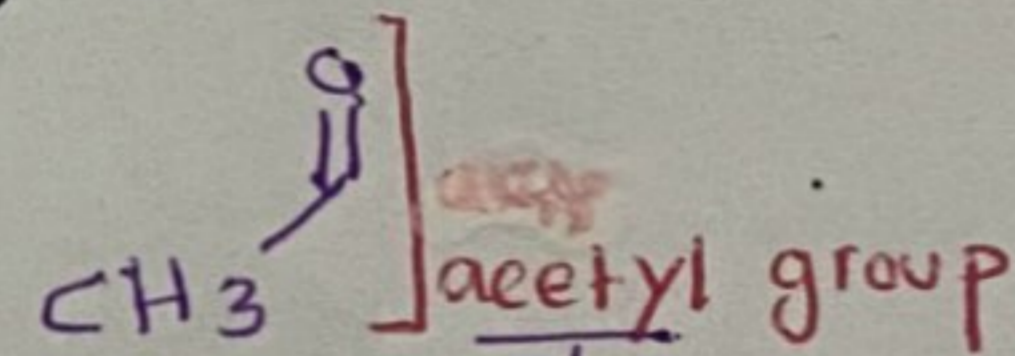
Amine لا درج لتي تتحول على
(1+2+3)



Secondary and tertiary amines are not acetylated.

Primary amine عادة يتكون ال aromatic أو

ex: - Sulfonamide
بصير على



acetyl group

ببطل عن مرتبة فقط

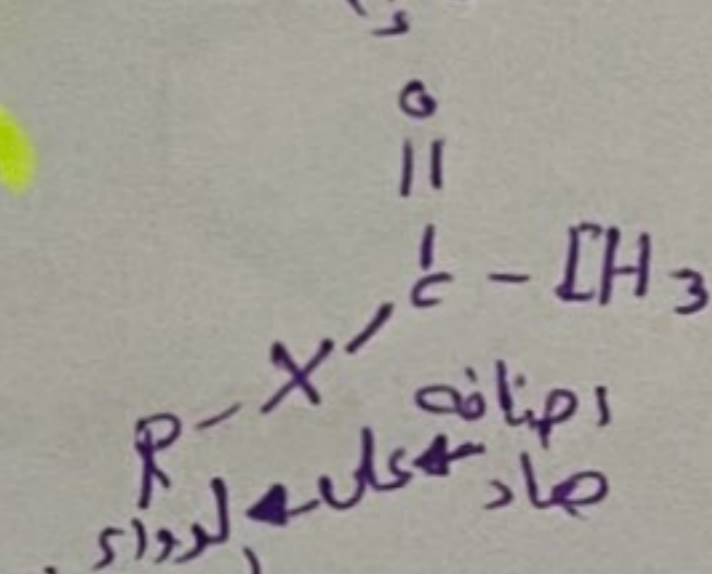
acylation

ببطل عن ايجافه اكثر من كربونين

acylation

acylation
هي عبارة عن ايجافه

acylation



معرفة حكيث شوي

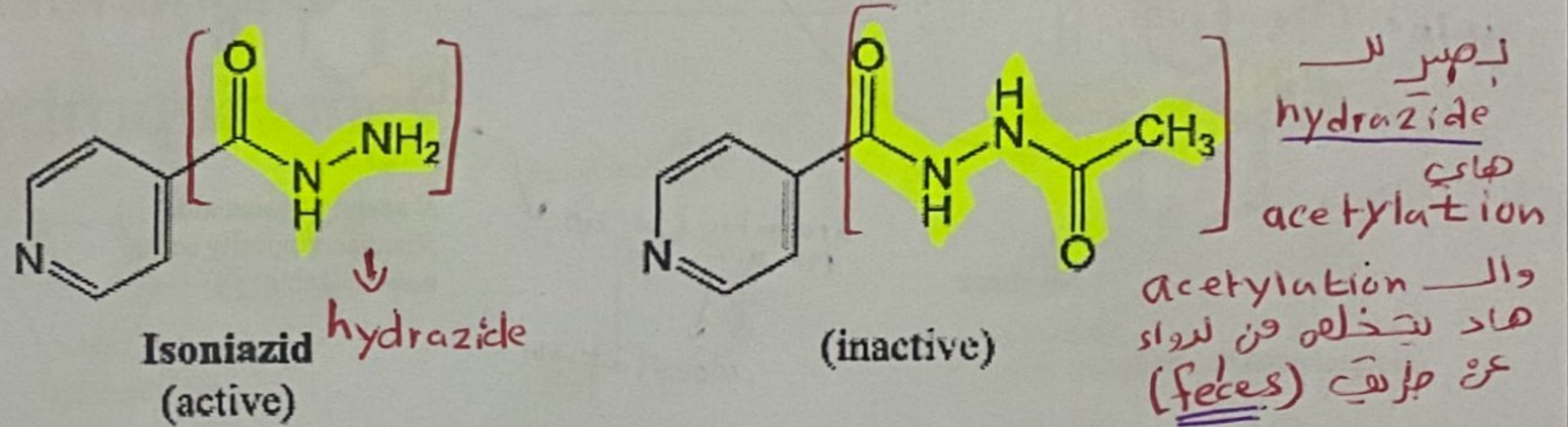
Important facts about acetylation

First Fact: People are divided into two groups according to the Acetylation:

- لازم نفهمه
- شوي يكون سطر
- دة اشارة على
- اعداد dose

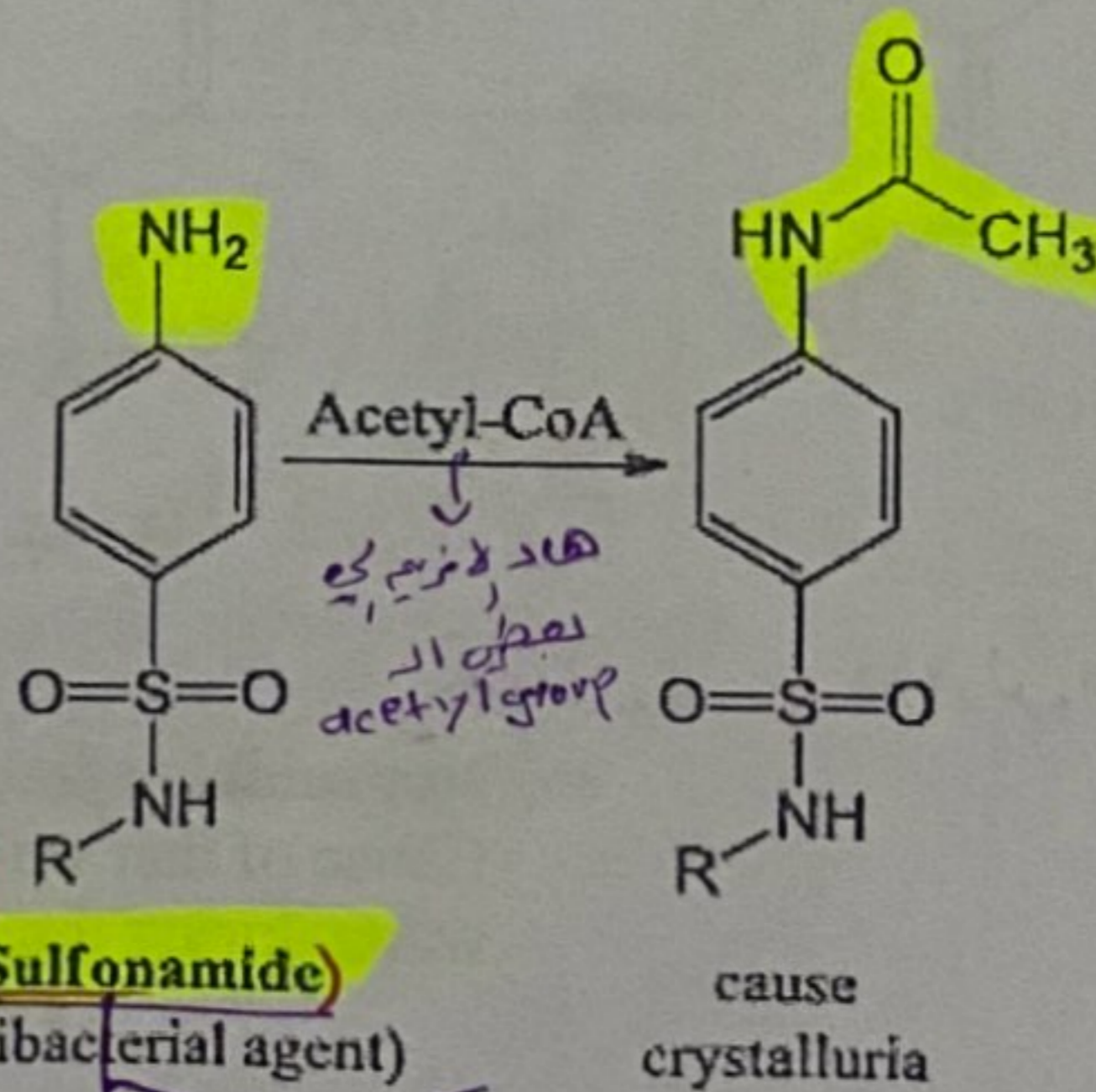
- A- Slow acetylators 50% → لأنه رجع بقدر له و اقتره طويله → جريه قليله
- B- Fast acetylators 50% → لأنه رجع بقدر له و اقتره قليله → جريه عاليه

- So before giving the Drug to a patient we should check if our patient is a slow or a fast acetylator especially if the drug is to be given for long period of time.
- For example "Isoniazide" drug that used for tuberculosis against Mycobacterium should be taken for long period of time (the treatment duration is 6 months to 2 years), so if the patient was fast acetylator we have to modify the dose (increase the dose) to accommodate the fact the individual is a fast acetylator while if the patient was a slow acetylator we have to decrease the dose.



Second fact

- We said that the aim of Phase 2 reactions is increasing the water solubility of the compounds, but in [Acetylation] we are adding an acetyl group to the compound which increases its lipophilicity!
- So Acetylation makes the compounds less water soluble and leads to their precipitation in the kidney and causes "Crystalluria" or "Kidney stones" حصى الكلى

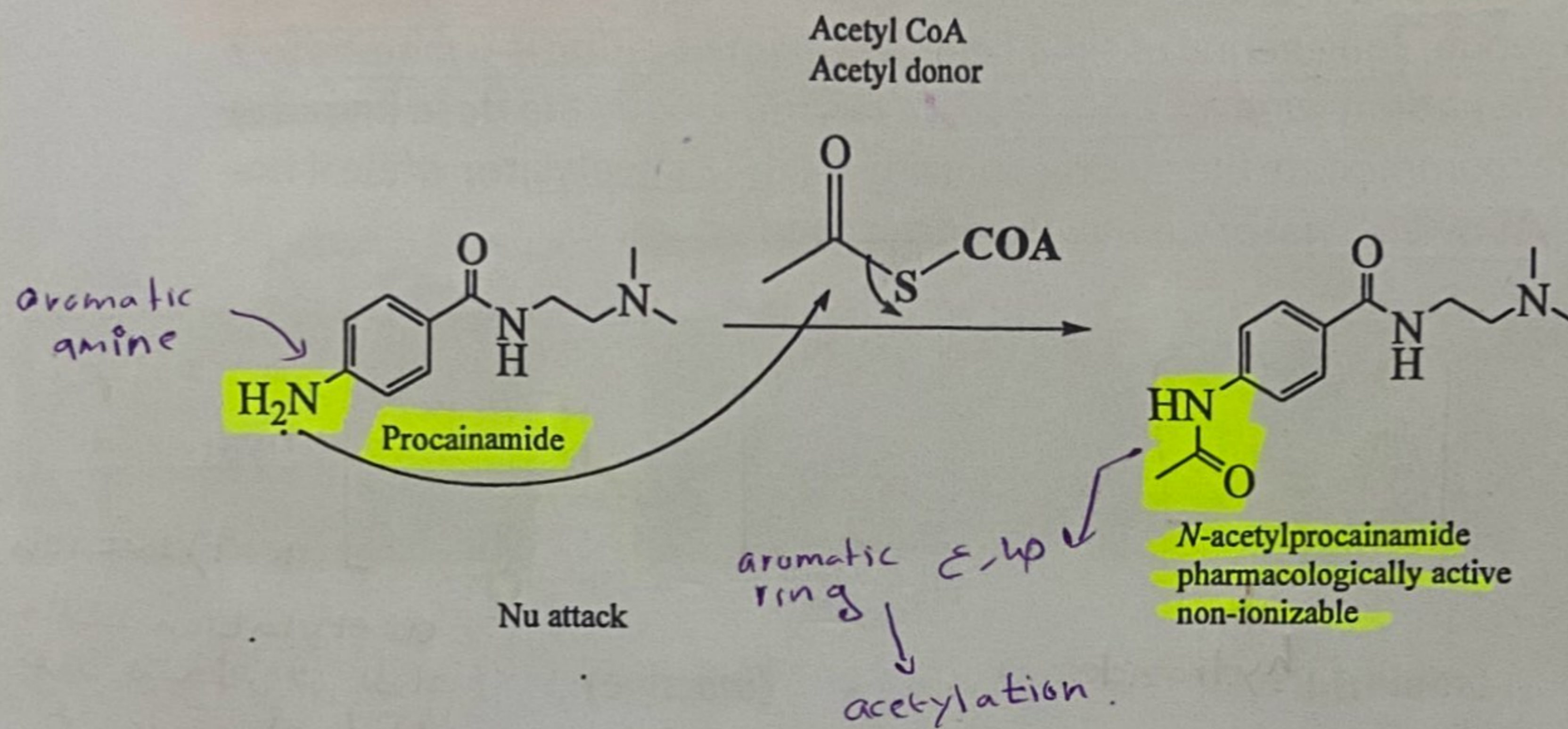


- 1) حاد الادوية الي بتبصر عليها
- 2) هاد الدواء يعالج العقابيات
- 3) الكماز البولي
- 4) هاد عاكس كل الـ conjugation الي صار قبل هاد تعلقه لذائبية
- 5) بتبصر بمرن اكي با خدوا هاد الدواء ليرتواص بغير
- 6) هوكبان الـ Sulfonamide بس بتبصر عليها
- 7) acetylation بغير الإنسان كونه لخص لكل أو crystalluria.

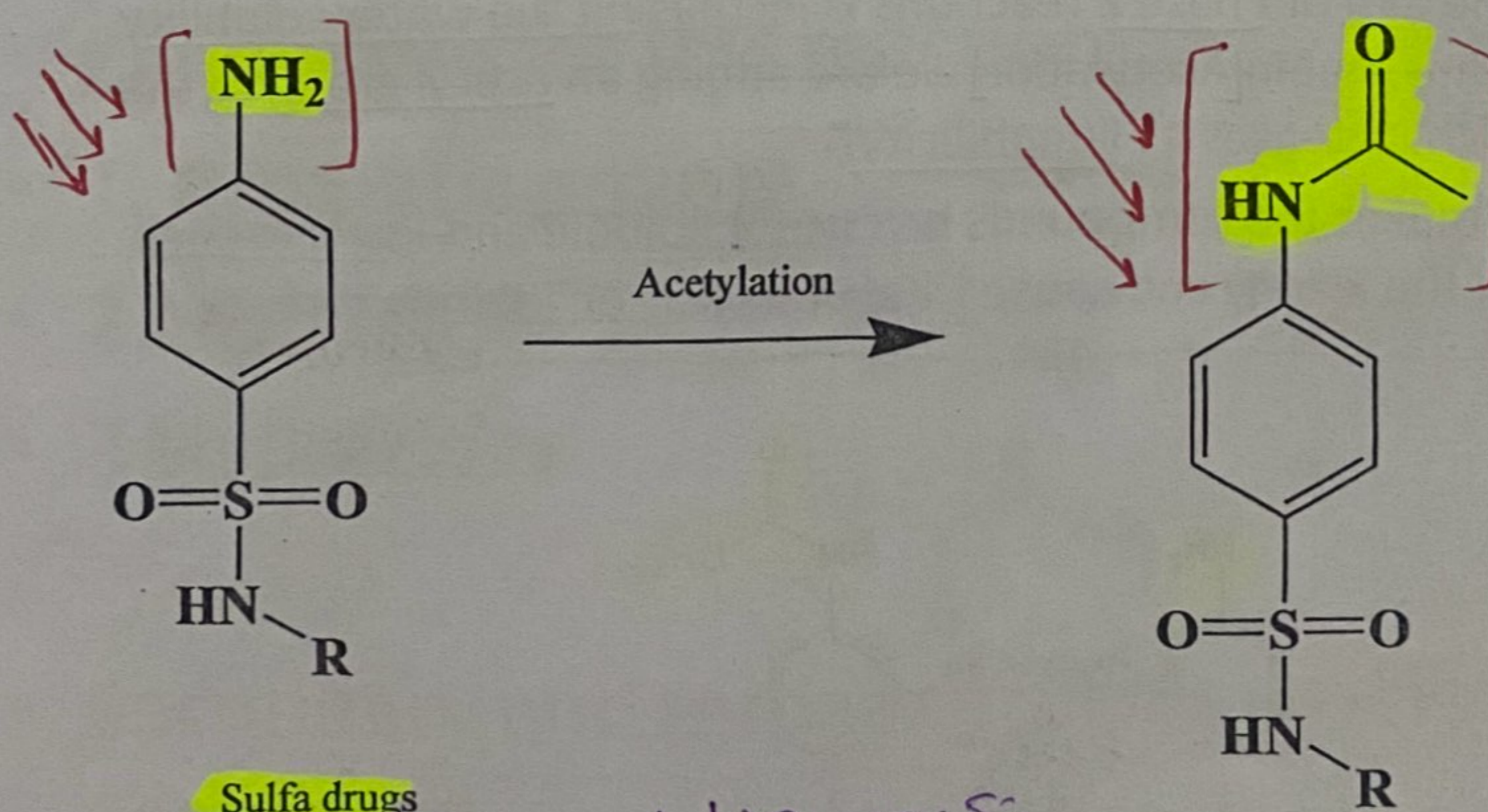
Example

* مثال رقم (2) على الادوية
التي يصير عليها
acetylation

- The product in this case is less soluble than the starting drug (special case)



Metabolism of sulfonamides Antibacterial drugs



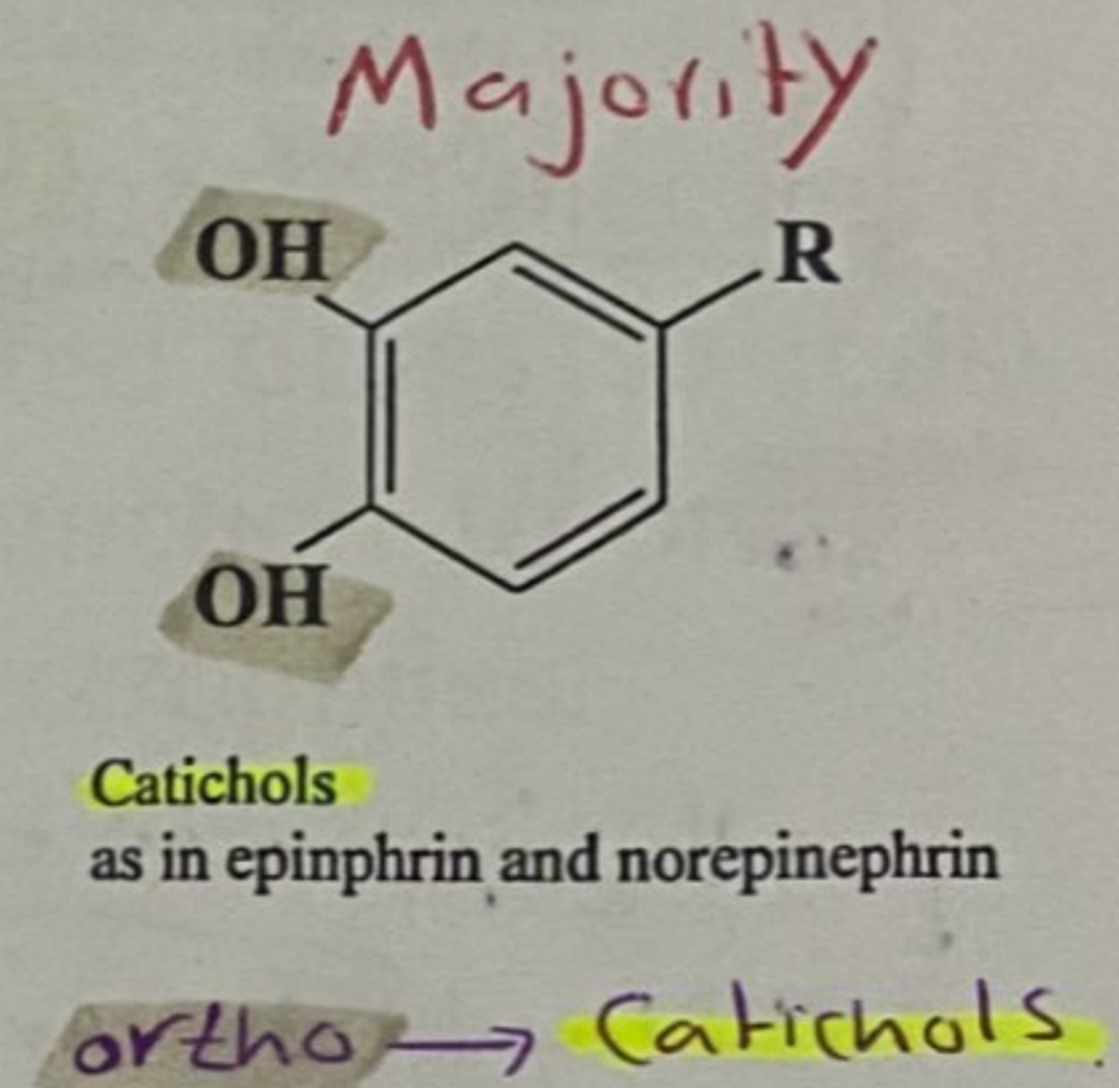
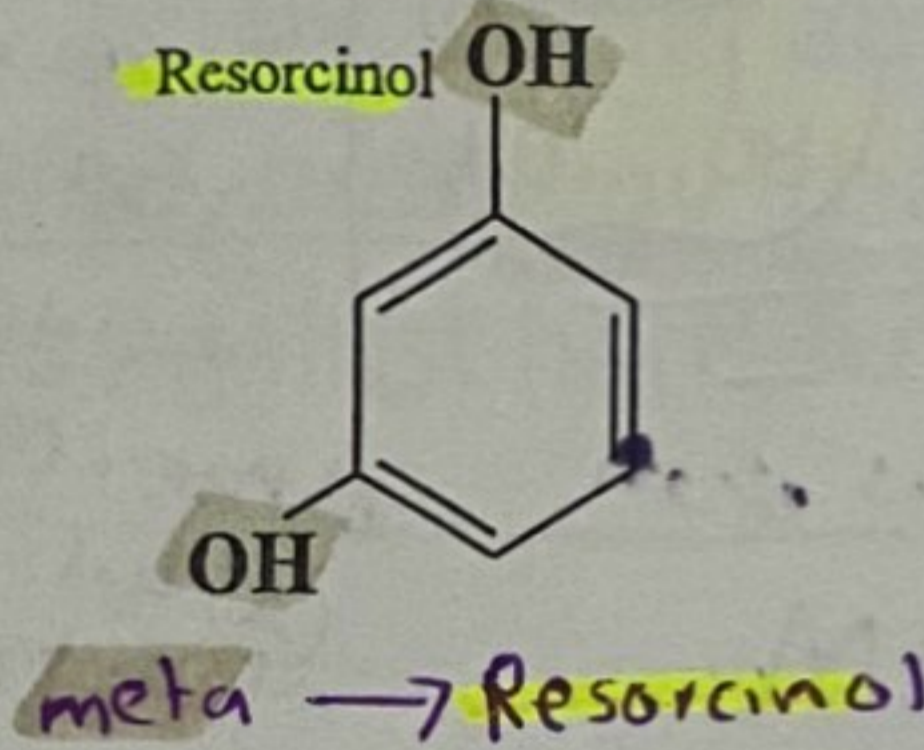
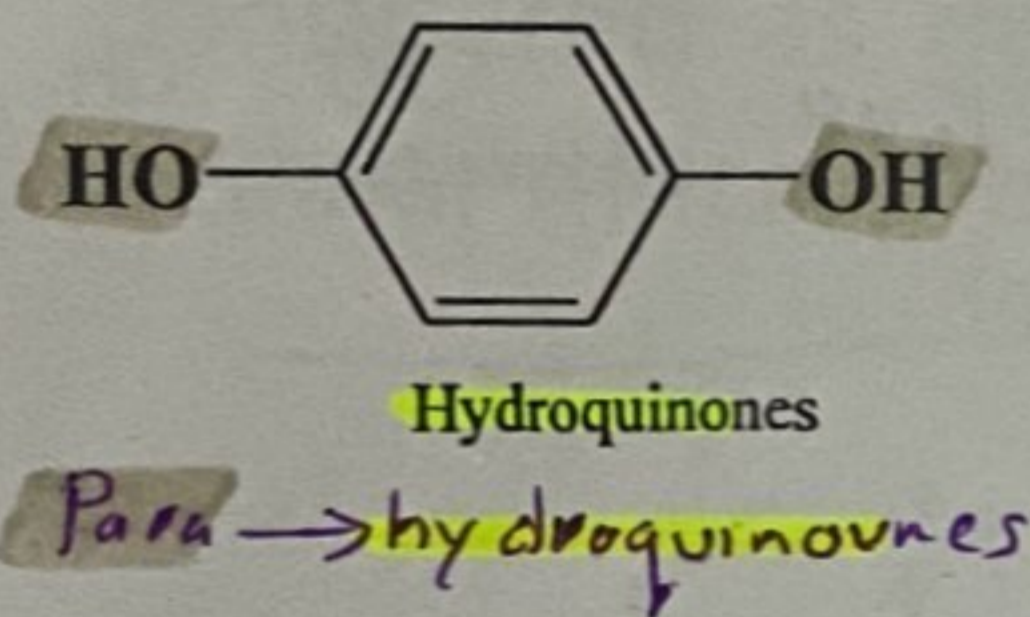
بشكله غير قابل للذوبان

Not soluble, precipitates in kidneys
Cause of that we recommend to drink a lot of water during the intake of such drug

مethyl group
 methyl donor

Methylation reaction

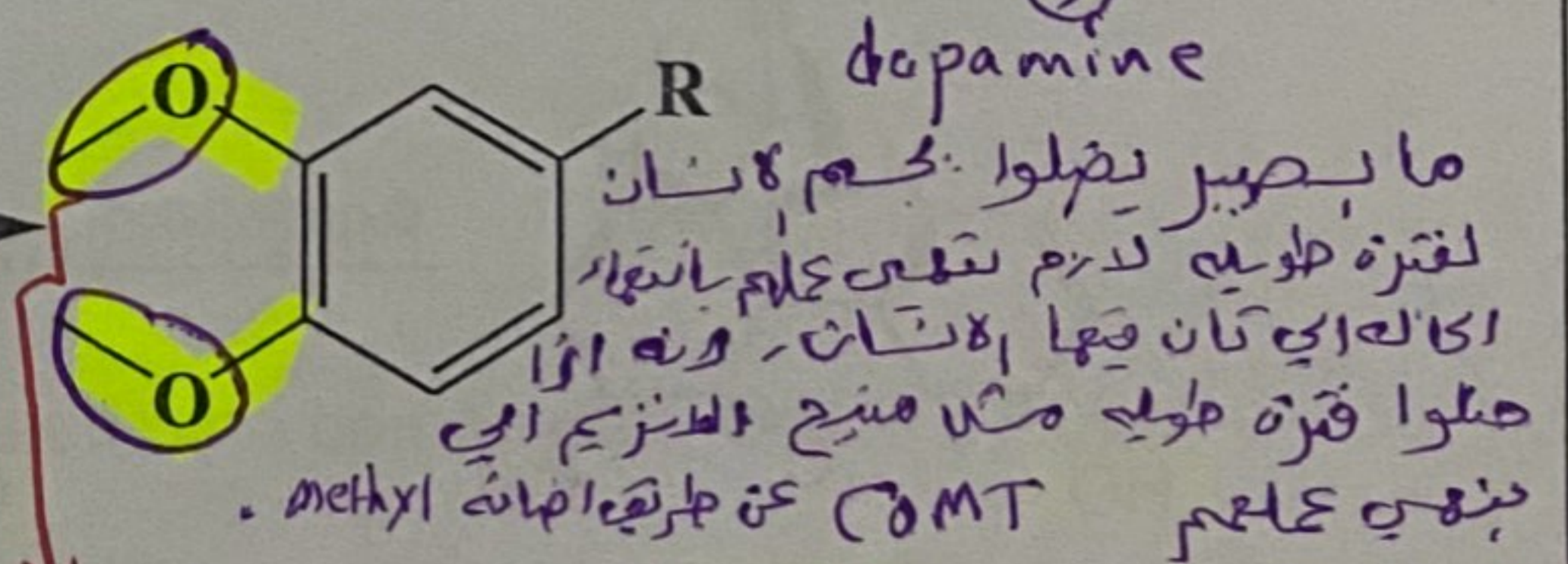
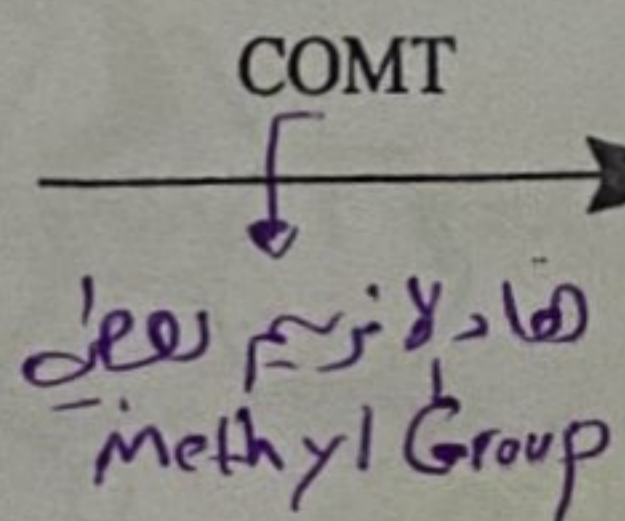
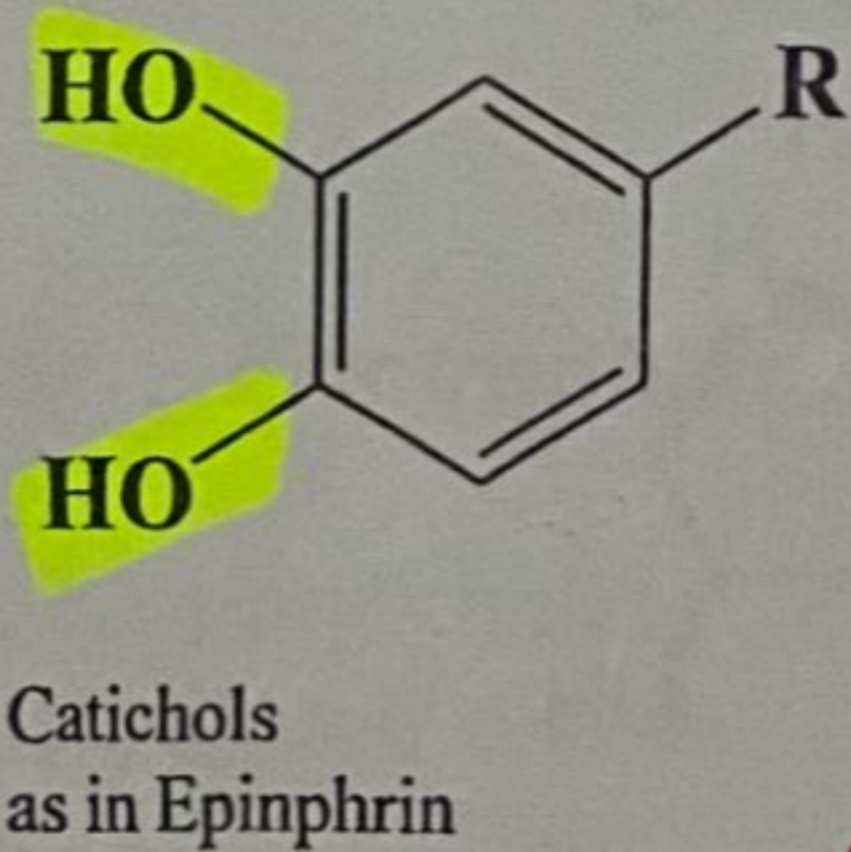
- Candidates for this reaction:
- ① Amines
- ② Alcohols
- ③ Catechols (majority)
- ⑤ Resorcinol
- ⑥ Hydroquinones



Methyl donor
 ① COMT
 ② SAM

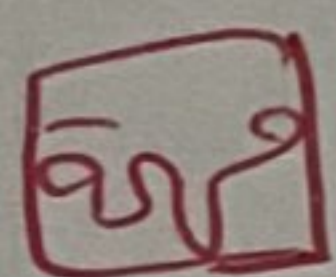
Methylation reaction

- ① COMT carries out O-methylation of such important neurotransmitters as (epinephrine) and (dopamine) and thus terminates their activity



* الجسم مبدل انزيم ال
 epinephrine

* مبادل انزيم COMT
 يضيف ال methyl group
 Catechols active form (epinephrine)



COMT: Catechols -O- methyl transferase enzyme helps in methylation reaction